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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/807,766	03/23/2004	James Patrick Dunn	R0170B-REG	4292

24372 7590 10/05/2006

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/807,766	DUNN ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *24-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 31-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/23, 7/27, & 10/1/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *PTO-413B*.

DETAILED ACTION

Claims 1-41 are currently pending in the instant application.

Election/Restrictions

The Markush group set forth in the claims includes both independent and distinct inventions, and patentably distinct compounds (or species) within each invention. However, this application discloses and claims a plurality of patentably distinct inventions far too numerous to list individually. Moreover, these inventions contain a plurality of patentably distinct compounds, also far too numerous to list individually. For these reasons provided below, restriction to one of the following inventions is required under 35 U.S.C. § 121, wherein a Group is a set of patentably distinct inventions of a broad statutory category (e.g. compounds, methods of making, methods of using, etc):

I. **Claims 1-23, and 31-41,** drawn to the compounds and compositions according to formula I, as well as the process of making them; classified in multiple subclasses of classes 548, 546, and 514.

II. **Claims 24-30,** drawn to methods of using the compounds, classified in class in multiple subclasses of class 514.

Rationale Establishing Patentable Distinctiveness Within Each Group

Each Group listed above is directed to or involves the use of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects

and reactive conditions (MPEP § 806.04, MPEP § 808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over either of the other inventions (Groups), i.e. *they are patentable over each other.* Chemical structures that are similar are presumed to function similarly, whereas chemical that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrefutable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in accordance with the holdings of ***Applications of Papesch***, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and ***In re Lalu***, 223 USPQ 1257 (Fed. Cir, 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the methods are drawn to a treatment of HIV infection, which can be affected using currently FDA-approved drugs.

Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Furthermore, these inventions require different searches and examination considerations. A search for one group that may potentially provide prior art for one group (anticipate or make obvious) would not necessarily anticipate or make obvious the other group (invention).

Therefore, because of the reasons given above, the restriction set forth is proper and not to restrict would impose a serious burden in the *search and examination* of this application.

During a telephone conversation with Brian Buckwalter on September 27, 2006 a provisional election was made without traverse to prosecute the invention of **Group I, Claims 1-23, and 31-41**. Affirmation of this election must be made by Applicant in replying to this Office action. **Claims 24-30** are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

Acknowledgement is made of Applicants' claim for benefit of US Provisional Patent Application 60/457,130, filed on March 24, 2003. Said claim has been made in the first paragraph of the Specification.

Information Disclosure Statement

Applicants' information disclosure statements (IDS), filed on March 23, 2004, July 27, 2004, and October 1, 2004 have been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Claim Rejections - 35 USC § 102

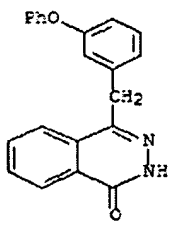
(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

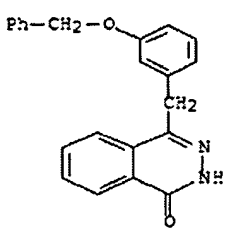
The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 2, and 9 are rejected under 35 U.S.C. 102(a & e) as being anticipated by Martin *et al.* (see IDS: WO 2002036576, 2002. Martin *et al.* discloses the compounds shown below, which read on said claims.

RN 420846-63-5



RN 420846-64-6



Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a compound or and acid addition salt thereof, does not reasonably provide enablement for a **hydrate, solvate,** or a **clathrate** of compound of the formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factual Basis:

The Specification has no working example of hydrate, solvate, or clathrate for a compound of formula (I); and some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed a solvate as evident from spectral data provided for these compounds.

Searching the pertinent art in the related pyrazole area did not result in support for such solvates of instantly claimed compounds. Searching the more general area of solvates resulted in a pertinent reference by West *et al.* (Solid Solutions, Solid State Chemistry and its applications, 1986). West shows a lack of predictability of the art in the solvate area.

Based on these two facts, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing a *prima facie* case is met.

Scope of Enablement rejection:

In evaluating enablement, several factors are to be considered. See *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. These factors include: 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, 7) the quantity of experimentation needed, and 8) the level of the skill in the art.

The nature of the invention and the state of the prior art:

The invention is drawn to compounds according to formula (I), or a pharmaceutically acceptable salt or solvate thereof. The specification is not adequately enabled as to how to make solvates for the compounds according to formula (I); the specification has no examples of hydrates, solvates, or clathrates of the instantly claimed compounds. The specification, on pages 17-18, recites definitions for hydrates, solvates, or clathrates, but there is no enabling disclosure of such solvates.

The compounds of formula (I) embrace pyrazole compounds substituted with a benzyl group, which is further substituted with an aryl or heteroaryl group via a linking atom or chain. Careful calculation of the number of compounds embraced in the instantly claimed formula (I) shows a large number of compounds. The term "substituted" (in all occurrences) embraces undefined number of variable groups and

thus, the genus embraced by Claim 1 is excessively large and there is no teaching of any hydrate, solvate, or clathrate of this large genus.

Search in the pertinent art, including water a solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that it is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of an organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of the West reference. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West states, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent." Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. In the instant case of solvate a similar reasoning therefore applies. Water is a solvate and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

Furthermore, an additional search resulted in Vippagunta *et al.* (*Advanced Drug Delivery Reviews,* 48, 3-26, **2001**), which clearly states that formation of solvates is unpredictable. See entire document, especially page 18, left column: section 3.4.

Vippagunta *et al.* states, "Each solid compound responds uniquely to the possible formation of solvates or hydrates and, hence, generalizations cannot be made for series of related compounds."

Ulrich (Chapter 4 in Crystallization, Kirk-Othmer Encyclopedia of Chemical Technology) provides that "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardness, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph."

The predictability or lack therof in the art:

The solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence, there should be adequate enabling disclosure in the specification with working examples.

The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds and not related to solvates or clathrates thereof. There is no example of hydrate, solvate, or clathrate of any of the instantly claimed compounds. Many of the exemplified compounds were shown in the specification that have come in contact with water and/or other solvents; however, there is no showing that these compounds formed hydrates, solvates, or clathrates. Therefore, it is clear that merely bringing the

compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them.

The presence or absence of working examples:

Determining if any particular substrate would form a solvate, hydrate, or clathrate would require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures, and other parameters. The experimentation is potentially open-ended. The direction concerning the hydrates is found on page 18, which simply states a definition. There is no working examples of any hydrate or solvate formed. The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. There should be some showing supporting that solvates of these compounds exist and therefore can be made.

The breadth of the claims and the quantity of experimentation needed:

The specification provides no support, as noted above, for compounds generically embraced in Claim 1, which would lead to a desired hydrate, solvate, or clathrate of the compounds according to formula (I). As noted above, the genus

embraces a large number of compounds, and therefore the claims are broad. The quantity of experimentation needed would be an undue burden on one skilled in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate of compounds of formula (I) embraced in the instant claims in view of the pertinent reference teachings.

Claims 1-23, and 31-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound according to the formula (I) in Claim 1 wherein, X^2 is **O**, **S**, or NR^7, it does not reasonably provide enablement for a compound having the structure in **Claim 1** wherein X^2 is **o-phenylene** or **1,2-cyclohexenylene**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factual Basis:

The Specification has no working example for a compound of formula (I) wherein X^2 is **o-phenylene** or **1,2-cyclohexenylene**; and furthermore, the methods described for the synthesis of formula (I), page 11 and **Claims 32-41**, are limited in scope for compounds according to the formula (I) in **Claim 1** wherein, X^2 is **O**, **S**, or NR^7.

Searching the pertinent art in the related pyrazole area wherein X^2 is **o-phenylene** or **1,2-cyclohexenylene** did not result in support for compounds wherein X^1 = $R^5S(O)_n$; R^5OCH_2; R^5CH_2O; $R^5S(O)_nCH_2$; R^5OCH_2; **and** NR^5R^6.

Based on these two facts, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing a *prima facie* case is met.

Scope of Enablement rejection:

In evaluating enablement, several factors are to be considered. See *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. These factors include: 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, 7) the quantity of experimentation needed, and 8) the level of the skill in the art.

The nature of the invention and the state of the prior art:

The invention is drawn to compounds according to formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the definitions of $\mathbf{X^1}$, $\mathbf{X^2}$, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, and $\mathbf{R^4}$ are defined therein. The specification is not adequately enabled as to how to make a compound of formula (I) wherein $\mathbf{X^2}$ is **o-phenylene** or **1,2-cyclohexenylene** and wherein $\mathbf{X^1 = R^5S(O)_n}$; $\mathbf{R^5OCH_2}$; $\mathbf{R^5CH_2O}$; $\mathbf{R^5S(O)_nCH_2}$; $\mathbf{R^5OCH_2}$; **and** $\mathbf{NR^5R^6}$. The specification has no examples wherein $\mathbf{X^2}$ is **o-phenylene** or **1,2-cyclohexenylene** for the instantly claimed compounds. The specification, throughout, recites examples of compounds as well as methods for the preparation thereof for a compound of formula (I) wherein $\mathbf{X^2}$ is **O**, **S**, and $\mathbf{NR^7}$.

The state of the prior art is such that it would enable one of skill in the art to make and use compounds according to formula (I) wherein $\mathbf{X^1}$ is an alkyl (substituted or unsubstituted), alkoxy, amino, sulfamide, and amide (C(O)NH-). However, these examples do not enable one to make a compound of formula (I) wherein $\mathbf{X^2}$ is o-phenylene or 1,2-cyclohexenylene and wherein $\mathbf{X^1}$ = $R^5S(O)_n$; R^5OCH_2; R^5CH_2O; $R^5S(O)_nCH_2$; R^5OCH_2; and NR^5R^6.

Careful calculation of the number of compounds embraced in the instantly claimed formula (I) shows a large number of compounds. Several combinations of the variable groups are present in the examples throughout the specification and the genus embraced by Claim 1 is excessively large, yet there is no teaching for a compound of formula (I) wherein $\mathbf{X^2}$ is o-phenylene or 1,2-cyclohexenylene and wherein $\mathbf{X^1}$ = $R^5S(O)_n$; R^5OCH_2; R^5CH_2O; $R^5S(O)_nCH_2$; R^5OCH_2; and NR^5R^6.

The level of predictability or lack thereof in the art:

The compounds according to formula (I) claimed by Applicant are not art-recognized compounds and hence, there should be adequate enabling disclosure in the specification with working examples.

The presence or absence of working examples:

The working examples set forth in the instant specification are directed to the compounds of the formula (I) for which $\mathbf{X^2}$ is **O**, **S**, and $\mathbf{NR^7}$. There has not been provided sufficient evidence that would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that *any* compound of formula (I) would indeed be able to be synthesized and used by means of the methods

outlined in the specification. No working examples are present in the instant specification for compounds of formula (I) wherein $\mathbf{X^2}$ is o-phenylene or 1,2-cyclohexenylene.

The amount of direction provided by the inventor:

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed invention commensurate in the scope with the instant claims. There is a lack of information pertaining to the synthesis of all compounds according to the formula (I) in which $\mathbf{X^2}$ is o-phenylene or 1,2-cyclohexenylene and $\mathbf{X^1}$ = $R^5S(O)_n$; R^5OCH_2; R^5CH_2O; $R^5S(O)_nCH_2$; R^5OCH_2; and NR^5R^6. The direction provided does not adequately represent the scope of **Claim 1** as written. The Examiner points out that all of the compounds in the tables as well as the synthetic procedures described throughout the specification provide guidance to the invention only when $\mathbf{X^2}$ is **O**, **S**, and $\mathbf{NR^7}$.

The breadth of the claims and the quantity of experimentation needed:

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation of any compound of **Claim 1**, as defined. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. Undue experimentation would include, for instance: the preparation of multiple synthetic outlines for each of the different definitions of $\mathbf{X^1}$ and $\mathbf{X^2}$; the preparation of the necessary starting materials required for each of the compounds according to the formula in **Claim 1** wherein $\mathbf{X^1}$ and $\mathbf{X^2}$ are different

functional groups, followed by attempts to prepare a desired product for each of the different X^1 and X^2 functional groups, subsequently followed by isolation, characterization, and testing the various compounds to determine if indeed have utility for the treatment of HIV infection.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

(for) Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: September 28, 2006